REMARKS

Claims 1, 47-64, 70, 74-81, 86-97, 99, 100, 103, 104 and 114-127 are currently active.

Antecedent support for the amendments to the claims is found on page 1, line 6.

The Examiner has rejected Claims 1, 47-64, 70, 74-81, 74-81, 86-97, 99, 100, 103, 104 and 114-127 as being unpatentable over Bisconte in view of Price. Applicants respectfully traverse this rejection. Bisconte does not teach or suggest tracking over time an individual cell in a group of cells in a dynamically controlled closed environment, as found in the claimed invention. All the teachings of Bisconte are directed to basically analysis and cloning of cellular cultures and for bacteriological analysis. Price teaches scanning cytometry to observe individual cell over time, but does not do so in a dynamically controlled closed environment.

In addition, both Bisconte and Price teach a plate 4 or a chamber that are inserted into their respective device for analysis, but are stored for cell incubation or growth in a totally distinct and separate location. Neither of these references teach or suggest the limitation of a "dynamically controlled closed environment in which the cells are grown", and

further "which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition", as found in Claim 47 of applicants.

Bisconte teaches that a plurality of cassettes 11 may be provided, each comprising its own plate 4, so as to facilitate storage particularly in a separate incubator (emphasis added), and so as to introduce into the first compartment 38, through the isothermal door 8 for closing the front face of enclosure 1, only the cassette corresponding to the predetermined experimental protocol or the desired cassette. See column 7, lines 4-11 of Bisconte. As more fully explained below, Price also simply teaches a glass chamber that is placed before the microscope for analysis, and also fails to teach or suggest a "dynamically controlled closed environment in which the cells are grown".

Bisconte discloses an automatic device for the analysis and cloning of cellular cultures as well as for bacteriological analysis. Bisconte teaches an enclosure 1 with isolating walls is divided into two compartments. There is compartment 3a which contains a plate 4, the motor unit 5, a microscope observation device 6 and an aspiration/injection device. Compartment 3b, which completely surrounds the compartment 3a, except at the level of the access door 8 formed in the front face of the enclosure 1. These compartments are separated by a metal wall 9 made from steel or aluminum. Forced air flow is established between the

two compartments. Flow of sterile and hot air passes through orifices in the bottom of compartment 3a. Plate 4 is made from a transparent material of good optical quality. Plate 4 may contain an external row of 16 microwells or 48 microwells depending on their diameter. Plate 4 is provided with a central opening for access to the aspirations/injection device in a discharge well 10 fixed to the lower wall of the first compartment 3a. The plate is disposed inside a cassette 11 square in shape which comprises a central circular recess 12 for housing plate 4. See column 6, lines 4-36. It is in compartment 3a that plate 4 is inserted for the desired experimental protocol to be performed. As mentioned above, and is clear from the text and figure 4, compartment 3a is not built for storage let alone a "dynamically controlled closed environment in which the cells are grown." Compartment 3a is just what Bisconte teaches it is, a receiving zone to insert a subject plate to perform the experimental protocols on the plate, and then for the plate to be removed and incubated in a separate location.

Plate 4 has a central opening for access to the aspirations/injection device in a discharge well 10 fixed to the lower wall of the first compartment 3a. A rotational drive for plate 4 is obtained by friction of the drive roller 14 and groove 13. See column 6, lines 33-55. Cassette 11 is provided with a transparent lid 16 fitted to the central opening in plate 44 to allow access of the aspiration/injection device into the discharge well 10. The lid 16 is provided with a radial window 17 for access of this aspiration/injection device into the microwells formed in plate 4 and aligned radially. See column 6, lines 65-68. Bisconte

teaches it is sometimes necessary to vary the height of plate 4, for placing the needle 23 of the aspiration device 7 in contact with the cells 24 adhering to the bottom of the marker well 25 or for perfecting the optical focusing knowing that the microscope device is fixed and preset. See column 7, lines 29-44. For obtaining the horizontal movement of a plate 4, the stepper motor 30 is caused to act on a gear projecting from the motor unit 5 and acting in its turn on a rack 18 fixed to the lower wall of housing 19. See column 7, lines 54-60. Bisconte teaches that the motor unit 5 allows for different types of sweeps of the microwells 25, such as a continuous plot with low magnification, a continuous plot with high magnification or a sweet following any zigzag plot. Column 8, lines 1-5. Continuous sweeps allow for densitimetric profiles to be obtained while zig zag sweeps allow for random preprogrammed field more corresponding to individual locations. See column 8, line 6-10.

Bisconte teaches a single lens/condenser pair is required. Lens 33 is placed in alignment with a condenser 34. The arrival of light into the condensers is provided by an optical fiber system 38. Pairs of lenses/condensers operate alternatively when the observation is to be made with low magnification with lens 33. An external prism sends a light beam onto the corresponding optical fiber. On leaving lens 33, the image is reflected by a mirror to the television camera placed either in compartment 3b or outside while extending the light guide G. In passing, the light rays pass through the Mir 42. See column 8, lines 25-45.

Bisconte teaches that the small volume of the compartment 3a provides automatic and constant humification by evaporation of the cellular medium contained in the microwell 25. The aspiration/injection device 7 is disposed in a vertical housing 45 formed in the upper wall of the first compartment 3a and cooperates with a device 46 for adjusting the height of nozzle 47. See column 9, lines 1-19. Aspiration takes place by retraction of piston 49 which sucks the membrane 50 through space 51. The depression thus created by membrane 50 is transmitted to space 52 and sucks up the liquid contained in the microwell 25. When the discharge well 10 is formed in the lower wall of compartment 3a, a cassette 11 is moved horizontally for aligning the central opening in plate 4 with nozzle 47 and well 10. The device 46 is then brought to a low position and collar 48 is applied against the upper surface of well 10 for providing ceiling. Piston 49 is then pushed back for driving out the liquid contained in 52. See column 9, lines 49-66.

Bisconte teaches that the main applications of the automatic device that is taught relate to cloning the analysis of materials or the analysis of bacteria. In regard to cloning, the plate 4 is disposed in cassette 11 after having seeded a single microwell 25. From the identification of the colonies, subcultures are formed and the other microwells of the plate are progressively supplied by means of the aspiration/injection device. In regard to the analysis of materials, measurements are able to be taken at very close intervals of the cellular kinetics. For analysis of bacteria, it occurs by colorimetric reactions. See column 10, lines 49-60. It

should be noted, that there is no discussion, nor teaching of any capability of tracking over time an individual cell in a group of cells in a dynamically controlled closed environment, as found in the claimed invention. All the teachings of Bisconte are directed to basically analysis and cloning of cellular cultures and for bacteriological analysis. See abstract. Accordingly, Bisconte does not teach or suggest the claimed invention of applicants.

Referring to Price, in pertinent part, Price teaches the cell culture chamber design consists of a glass slide and coverslip of equal rectangular dimensions held 250 μM apart by a retainer made of Teflon. This retainer may contain access ports for the input and output of medium and the placement of a thermistor type temperature probe. Upper and lower aluminum rectangular frames hold the glass pieces of the Teflon retainer with enough pressure to create a seal. A thin film of vacuum grease may be applied between the Teflon and glass pieces if necessary. All medium infusion will be through the Teflon retainer and will contact only the glass once inside the chamber to avoid metallic ion toxicity. Temperature is controlled by use of a probe in direct contact with the control culture medium and a heating element in the baseplate of the stage. The design allows for assembly prior to autoclaving to minimize the kind of handling that compromises stability. Cells are introduced by infusion and infusion stopped long enough for cell attachment. This design will simplify handling and facilitate multi-day microscope stage culturing. See column 23, lines 19-44 of Price.

From the aforementioned description, it is clear that Price teaches a very small glass chamber that is also moved from another location to the microscope for scanning cytometry and then removed and put back to its storage location remote and apart from the microscope. It is also clear from the above, there is no teaching or suggestion that the environment of the chamber taught by Price is in any way dynamically controlled while "each individual cell of the plurality of cells is individually examined over time while the environment is dynamically controlled and maintained in the desired condition," as found in claim 47.

Furthermore, Price teaches that the retainer may contain access ports for the input and output of medium, but does not teach anywhere the use of "a robotic arm for dispensing and aspirating different material to each cell of the plurality of cells while the cells are disposed in the dynamically closed environment in the biochamber".

As mentioned above, the Examiner's rejection based on combining the teachings of Bisconte with the teachings of Price ignores the context in which each of these teachings are found. Patent law requires that the context of the teachings the examiner relies upon the taken into account.

The Examiner cannot ignore that Price teaches a very small glass chamber that is moved from another location to the microscope for analysis. This glass chamber is not dynamically controlled at all and is not designed for a robotic arm to dispense or aspirate material into or from it. At minimum, it would require one skilled in the art to have to experiment, research and develop a new design to allow for these features. This does not even speak yet to somehow making the new design work with the system of Bisconte. This only supports a finding of nonobviousness. It also further supports a finding of using hindsight from applicants' claimed invention to be motivated to do the same since there is no indication of such a need in Price or in Bisconte for that matter. The use of hindsight is not patent law.

In regard to Bisconte, the question arises how are the teachings of Price, in the context in which they are found, applied to the system taught by Bisconte. Price teaches a very specific structure for the chamber so that scanning cytometry can be performed. It is specifically the scanning cytometry that Price teaches which allows cells to be followed over time. Bisconte does not teach the use of scanning cytometry, or the capability of performing scanning cytometry, and thus no structure to support scanning cytometry. Bisconte does teach a microscope, but there is no teaching or capability of performing the more complex technique of scanning cytometry. Thus, the specific chamber taught by Price must somehow or other be accommodated by Bisconte to allow for the scanning cytometry. Furthermore, to take it further in regard to the context of Bisconte, one of the key features of Bisconte, it is

submitted, is the aspiration device 7. A plate 4 taught by Bisconte has a radial window 17 for access of the aspiration/injection device into the micro wells formed in plate 4 in the line radially. See column 7, lines 1-3. So that the context and key operation of Bisconte is respected, the chamber taught by Price must in some way be designed to accommodate such an aspiration device 7. It is respectfully submitted by applicants, it is not clear to them at all how such a redesign would occur to allow the teachings of Price to be applied to the teachings of Bisconte, and still have Bisconte operate in its intended function and purpose.

In addition, as mentioned above, there must be some teaching or suggestion to combine the teachings of these two references, and there is none. There is no teaching or suggestion and Bisconte of the needs to individually examined over time each individual cell of a plurality of cells, as found in Claim 47 of applicants. In fact, as has been already stated, Bisconte is only concerned with cell cultures, not at all lists individual cells. Price provides no teaching or suggestion, or even the need, of examining over time each individual cell of a plurality of cells in a dynamically controlled environment.

Even the problems that Bisconte and Price solve are distinct from each other and from applicants' claimed invention. Applicants' claimed invention is directed to examining each cell of a plurality of cells individually over time in a dynamically controlled closed environment. Bisconte is directed to analyzing and cloning cellular cultures. Price is directed

to increasing the efficiency of scanning cytometry. Accordingly, since the problems that the two references solve are distinct from each other and from the problem that applicants' claimed invention cells, there is no basis or support from their respective problems to cause one skilled in the art to arrive at applicants' claimed invention by combining the teachings of Price and Bisconte. For this reason, the combination of Price and Bisconte, under patent law, do not arrive at applicants' claimed invention.

It is respectfully submitted the Examiner is using the limitations of applicants' claims as a roadmap to find the limitations in various disparate references, and supposedly having found them, concluding that applicants' claimed invention is arrived at. This is the use of hindsight, which is contrary to patent law. It is only this hindsight, that provides any explanation as to why Price and Bisconte would be combined. Accordingly, Claim 47 is patentable over the applied art of record. Claims 49-51, 57, 59, 63, 64, 66 and 70-75 are dependent apparent Claim 47 and are patentable for the reasons Claim 47 is patentable.

It should also be noted that the chamber of Price and the plate of Bisconte are in conflict. The chamber of Price is taught to be closed and sealed and very thin so cytometry can be successfully performed. In contrast, the plate of Bisconte is very thick an open to hold the wells and aspirate/dispense from or into the wells. Based on the teachings of Price, it is submitted such a plate design of Bisconte would not allow for successful cytometry, so the

tracking of a cell over time could not occur. This follows because Bisconte is concerned only with cell cultures. The teaching of a thin sealed chamber by Price thus teaches away from a thick open plate of Bisconte, and for this reason alone, one skilled in the art would not look or consider to combine the teachings of Price with the teachings of Bisconte.

In view of the foregoing amendments and remarks, it is respectfully requested that Claims 1, 47-64, 70, 74-81, 86-97, 99, 100, 103, 104 and 114-127, now in this application be allowed.

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